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ABSTRACTS OF RECENT CHINESE PUBLICATIONS ON MALARIA[1] (VIII)

62. Li, D. M. et al. Electron microscopy of erythrocytic stages of Plasmodium falciparum in continuous cultivation. Chinese Journal of Microbiology and Immunology, 1981, 1 (4): 291

Electron microscopy was used to study the knobs on the surface of erythrocytes infected with Plasmodium falciparum isolated from Hainan and grown in vitro for 18 to 526 days. Results showed that with a prolonged period of cultivation the knobs on the surface of erythrocytes infected with trophozoites or schizonts had a tendency to disappear. It is therefore considered important that attention be paid to the age of cultivated parasites when carrying out studies on malaria vaccine and other immunological problems in view of the well-known immunogenicity of the knobs.

63. Zheng, X. Y. et al. Synthesis of a new antimalarial drug pyronaridine and its analogues. Acta Pharmaceutica Sinica, 1982, 17 (2): 118 (In Chinese, with English abstract)

Based on the structure-activity relationship of certain antimalarial drugs, a new compound 2-methoxy-7-chloro-10-/3',5-bis (pyrrolidino-methy)-4'-hydroxyanilino/ benzo /b/ 1,5-naphthyridine (I), coded 7351, was synthesized and named pyronaridine. This compound exhibited a high schizontocidal activity and low toxicity. Since then, a series of analogues II, 2-substituent-7-chloro-10-/3',5'-bis- or 3'-mono-(substituted aminomethyl)-4'- or 2'-hydroxyanilino/ benzo /b/-1,5-naphthyridines have been synthesized.

Compound I and its analogues II were prepared with 2-substituent-5-aminopyridines as intermediates. These intermediates were condensed with 2,4-dichlorobenzoic acid to give 2-substituent-5-)2-carboxy-5-chloroanilino) pyridines which were cyclized in the presence of phosphorus oxychloride. The cyclized products 2-substituent-7,10-dichlorobenzo/b/ 1, 5-naphthyridines, were subsequently condensed with 4- or 2-hydroxyaniline to form 2-substituent-7-chloro-10(4'- or 2'-hydroxyanilino) benzo/b/ 1,5-naphthyridines, the latter being finally reacted with Mannich reagents to yield the desired compound I and its analogues II.

Most of the analogues II were effective in varying degrees in the murine blood schizontocidal test, and analogues $II_{1-6,9,10}$ were as effective as compound I. Moreover, compound I and analogues $II_{1,3,5,6,9,10,12,15}$ were also highly effective in the Plasmodium yoelii-Anopheles stephensi mouse system, their potency being superior to that of primaquine. It is worth noting that the substituted benzo-/b/ 1,5-naphthyridines were effective, not only against P. berghei infection by blood transmission, but also against P. yoelii infection through sporozoite inoculation.

[1] The WHO/MAL series has been chosen as a vehicle for issuing abstracts or translations in English of papers on malaria published in the Chinese medical and scientific press as most of this material is not readily available to interested readers outside China. The numbering of the abstracts in this document is consecutive to that of the abstracts given in the previous WHO/MAL/82.985.

64. Chen, C. et al. Studies on new antimalarials. Synthesis of heterocyclic compounds carrying double Mannich basic chains of p-aminophenol. Acta Pharmaceutica Sinica, 1982, 17 (2): 112 (In Chinese, with English abstract)

This paper describes the preparation of heterocyclic compounds V_{1-19} carrying double Mannich basic side chains of p-aminophenol. These heterocyclic nuclei are: benzo [g] quinoline; 1,5-naphthyridine, pyrido [2,3-d] pyrimidine, benzo [c] acridine, pyrido [2,3-c] acridine, and pyrido [2,3-e] acridine. Compounds V_{1-19} were synthesized from the heterocyclic intermediates a-f by condensing with p-aminophenol. Products VI carrying p-aminophenol reacted further with Mannich reagents to yield the desired compounds.

Compounds $V_{1-3,6,8-15,19}$ were tested for blood schizontocidal activity against Plasmodium berghei in mice and results showed that compounds V1-3,8,10,12,19 were rather effective. In the P. yoelii-Anopheles stephensi mouse model, compounds $V_{4-10,16,19}$ did not show any activity.

65. Zhao, D. C. et al. Studies on antimalarials. II. Synthesis of α-alkylaminomethyl-1, 6-dichloro-4-fluorenemethanols. Acta Pharmaceutica Sinica, 1982, 17 (1): 28 (In Chinese, with English abstract)

The preceding paper of this series described the antimalarial activity of α-alkylaminomethyl-halogenated-4-fluorenemethanols (see WHO/MAL/82.985, abstract No.54). In a further search for antimalarials with higher activity and lower toxicity, another fourteen α-alkylaminomethyl-1,6-dichloro-4-fluorenemethanols (II) were synthesized for biological evaluation. Preliminary results showed that nine of the compounds were active at 25 mg/kg and one of these suppressed parasitaemia at 2.5 mg/kg.

66. Li, F. L. et al. Studies on antimalarials. Synthesis of 4-arylamino-2-tert-butylaminomethyl phenols. Acta Pharmaceutica Sinica, 1982, 17 (1): 77 (In Chinese, with English abstract)

Six compounds of 4-arylamino-2-tert-butylaminomethyl phenols were synthesized and screened for their activity against established infections with chloroquine-sensitive and chloroquine-resistant strains of Plasmodium berghei in mice. All these compounds exhibited a marked antimalarial effect except for compound IV. Two of these compounds, 4-(7-chloro-4-quinolinylamino)-2-tert-butylaminomethyl-5,6,7,8-tetra-hydro-1-naphthol (compound IV_a) and 4-(2-methoxy-7-chloro-10-benzo-[b]-1,5-naphthyridinylamino)-2-tert-butyl-amino-O-cresol (compound V_c) were more effective than the others. The ED_{50} (dose which causes 50% reduction of the parasites) of compound IV_a against infections with the chloroquine-sensitive strain of P. berghei was 0.33 mg/kg after subcutaneous administration; the ED_{50} of compound V_c against infections with the chloroquine-resistant strain was 1-5 mg/kg, while the ED_{50}s of chloroquine were 1.12 and 34.5 mg/kg respectively against the two strains of P. berghei. A systematic study of these compounds is in progress.

67. Zhang, Y. D. et al. Determination of O-methyldihydroartemisinine (artemether) in plasma by quantitative thin layer chromatography (TLC) scanning technique. Acta Pharmaceutica Sinica, 1982, 17 (3): 212 (In Chinese, with English abstract)

O-methyldihydroartimisinine (artemether) is one of the effective derivatives of Qinghaosu. It has been demonstrated that this compound is a much more potent antimalarial than artemisinine. In order to carry out studies on its physiological disposition and establish the dosage regimen on a rational basis, a sensitive and specific bioanalytical method is required. Determination of artemether in rabbit plasma by quantitative thin layer chromatography (TLC) showed that the method seemed to have quite a good specificity. The lower limit of detection was 0.1 μg and a total recovery of over 83% was obtained. The results showed that this method meets well the needs of preclinical studies on artemether.

68. Cai, X. Z. et al. Investigation of the sensitivity of Plasmodium falciparum to chloroquine at Qianjia, Hainan Island. Chinese Journal of Preventive Medicine, 1982, 16 (1): 6 (In Chinese, with English abstract)

Using the method outlined in the WHO Technical Report Series No. 529 (1973), 93 subtertian malaria patients from Qianjia district in the south-western part of Hainan Island were investigated from June to November 1975. Different degrees of chloroquine-resistance were found in 76 cases, i.e. 40 cases (43%) at RI level, 24 cases (26%) at RII level and 12 cases (13%) at RIII level. The remaining 17 cases (18%) appeared to be sensitive. The level of immunity of the patients was in inverse proportion to the level of resistance of the malaria parasite Plasmodium falciparum. The remission rate of fever was roughly parallel to the resistance level. P. falciparum which showed resistance to chloroquine was, like the chloroquine-resistant strains of South-East Asia, also resistant to pyrimethamine (150 mg/3 days).

69. Guan, W. B. et al. An in vitro microtechnique for determination of the antimalarial activity of drugs. Acta Pharmaceutica Sinica, 1982, 17 (2): 139 (In Chinese, with English abstract)

An in vitro microtechnique was developed for the determination of antimalarial activity of drugs on Plasmodium falciparum strain FCC_1. Plastic plates, with 40 wells per plate, were used. Each well (6.7 mm in diameter and 10 mm in depth) held 180 µl of RPMI 1640 culture medium containing 2.5% red blood cells (infection rate about 1%) and 20 µl of the test drug solution in glucose saline. The cultures were incubated at 36-37°C in candle-jar for 48 hours, according to the Trager & Jensen method, without changing the medium during the incubation period. In the control, the parasites multiplied at an increasing rate going from 1.05 ± 0.10% to 3.75 ± 0.89%. The ED_{50} of the tested drug was calculated as the dose which causes 50% reduction of the parasites as compared with the control. The mean ED_{50} of chloroquine was 4.40 ± 0.82% ng/ml (5.59-3.36 ng/ml). This method is considered to be useful and reproducible for testing antimalarials directly with human malaria parasites.

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